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TRANSPOSITION OF THE GREAT VESSELS WITH PATENT DUCTUS ARTERIOSUS

Juan F. Jimenez, M.D.*

Because of the development of new instruments and surgical techniques for the correction of certain congenital heart defects, the accurate anatomical diagnosis of congenital heart disease has become a *must* in pediatric cardiology.

White estimates the importance of history at 50 per cent, physical examination 30 per cent, electrocardiogram 10 per cent, x-ray studies 5 per cent, and other studies 5 per cent in arriving at a diagnosis. Gibson emphasizes a good appraisal of the patient's general appearance, state of nutrition, presence of deformities, and color of the skin. Cyanosis is one of the most important signs, and special emphasis must be given to its time of appearance and distribution. Marked cyanosis from birth would suggest a diagnosis of tetralogy of Fallot, tricuspid atresia, pulmonary stenosis with septal defect, transposition of the great vessels, or persistent truncus arteriosus. Cyanosis after birth suggests Eisenmenger's complex or Taussig-Bing anomaly. Distinctly greater cyanosis of the upper extremities than lower extremities is found in transposition of the great vessels with patent ductus arteriosus because in this condition oxygenated blood from the pulmonary artery enters the descending aorta and increases the oxygen content of the blood in the lower extremities. Greater cyanosis in the lower extremities than the upper extremities is present in coarctation of the aorta with patent ductus arteriosus. In this condition venous blood from the pulmonary artery is shunted to the descending aorta, diminishing the oxygen content of the blood in the lower extremities.

The following case report illustrates the importance of the distribution of cyanosis in making a diagnosis.

CASE REPORT

W. W., a 2 month old colored male infant was admitted to Children's Hospital September 28, 1955 with acute respiratory distress. The infant had not been well since birth. He had had circumoral pallor, fatigability and dyspnea during feedings, and failure to thrive. Twenty-four hours before admission sudden respiratory distress developed, and was accompanied by moaning and grunting. He was brought to the Out Patient Department and was admitted to the hospital.

This infant was the product of a full term pregnancy and a normal spontaneous delivery. His birth weight was 7 pounds 8½ ounces. The mother was healthy and had had no illness or complication in her prenatal period. Four siblings were living and well.

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* Formerly Assistant Chief Resident, Children's Hospital.

Physical examination revealed a poorly nourished cyanotic infant in acute respiratory distress. His temperature was 99.6 F., pulse 160 per minute, and respirations 60 per minute. The chest was symmetrical, there were intercostal and substernal retractions on inspiration and fine crepitant rales and wheezes over the entire lung field. The point of maximal impulse was in the fourth left intercostal space lateral to the midclavicular line. The heart rate was 140 per minute and regular. A grade III, harsh systolic murmur was heard over the precordium with radiation to the back. The pulmonic second sound was accentuated. The abdomen was distended, and the liver margin three cm. below the right costal margin. The spleen and kidneys were not felt. There was cyanosis of the nail beds, more marked in the upper extremities. A vigorous femoral pulse was felt bilaterally.

X-ray of the chest showed congestion of the lungs and dilatation of the cardiac silhouette with diminution in the size of the great vessels. An electrocardiogram showed evidence of right ventricular strain.

A diagnosis was made of transposition of the great vessels with patent ductus arteriosus, impending heart failure, and bronchiolitis.

The infant was placed in a humidified oxygen tent (croupette) with detergent mist and oxytetracycline was given intramuscularly. He was digitalized with lanatoside, 0.1 mg., intravenously, and was given 0.03 mg. of digitoxin four hours later. This was repeated three times at eight hour intervals, and he was given a maintenance dose of 0.1 mg. of oral Digalen ® daily. On the third day dyspnea diminished and cyanosis decreased, especially in the lower extremities. The patient was able to take liquids by mouth and to rest better. Fluoroscopy showed an egg shaped heart with a narrow vascular pedicle and clear lung fields. Electrocardiogram on the sixth day of illness showed sinus bradycardia and suggestion of abnormal myocardium. On the tenth day of illness the infant had severe respiratory distress which persisted despite continuing supportive therapy. On the eleventh day the infant stopped breathing and did not respond to artificial respiration.

At post mortem examination, the body was that of a poorly nourished, poorly developed 2 month old colored male infant, with cyanosis of the lips and finger nails. Lividity and rigor mortis were present. The lungs were mottled pink and purplish except for the left lower lobe which was dark blue and airless. Pulmonary edema and interstitial pneumonia were seen microscopically. The pericardium was smooth and the coronary vessels and their branches were distended and prominent. The myocardium was congested and pink, and the endocardium grayish pink. The papillary muscles and chordae tendineae were intact and the valves essentially normal. There was marked dilatation of both ventricles. The interventricular septum was intact. The foramen ovale was patent and measured 0.2 x 0.1 cm. The aorta originated directly from the right ventricle, the pulmonary artery from the left ventricle. The ductus arteriosus was patent and was 0.25 cm. in diameter. There was acute passive congestion of the brain, lungs, liver, spleen, and kidneys.

Final Pathologic diagnoses:

1. Congenital heart disease
   A) Transposition of great vessels
   B) Patent foramen ovale and ductus arteriosus
   C) Hypertrophy of left and right ventricles
2. Pulmonary edema
3. Interstitial pneumonia
4. Acute passive congestion of the brain, lungs, liver, spleen and kidney.

DISCUSSION

Transposition of the great vessels is the second most common cause of congenital cyanotic heart disease. It is more common in boys than in girls. Cyanosis is present at birth and death usually occurs before 6 months of age. Life after birth is only possible if there is a communication between the systemic and pulmonary circulations. Hanlon and Blalock emphasized that the larger the communication between the right and left sides of the heart, the longer the time of survival. The most common intracardiac communication is a patent foramen ovale and next a ventricular septal defect. Patent ductus arteriosus is present in about two-thirds of the cases. A less common communication is an abnormal venous return with a systemic vein emptying into the left atrium or a pulmonary vein into the right atrium. Bronchial arteries are able to carry a large amount of the blood between the two systems.

The most important physical sign besides cyanosis is a greatly accentuated second heart sound over the pulmonic area. The murmur varies in nature and may not be heard at all. Roentgen study shows an egg shaped dilated heart with a narrow base in the AP view and concavity of the pulmonary artery segment. The left anterior oblique view shows widening of the base of the heart. The pulmonary vascular markings are increased. Electrocardiogram shows right heart strain. Angiocardiogram shows the aorta filling from the right ventricle and the pulmonary artery filling about one second later from the left ventricle. Cardiac catheterization shows a septal defect and a high pressure in the right ventricle. Evaluation of the shunt by gas analysis is uncertain because of variation in the shunts.

Several surgical procedures have been tried to correct this defect, but to the present time without success.

SUMMARY

As in this case of transposition of the great vessels with patent ductus arteriosus, an anatomical diagnosis can be made on the basis of cyanosis from birth, greater in the upper extremities, accentuated pulmonic second heart sound, a harsh precordial systolic murmur, and the egg shaped appearance of the heart on x-ray examination. Transposition is the second most common cause of cyanotic congenital heart disease and patent ductus arteriosus is present in two-thirds of the cases.

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THE NEPHROTIC SYNDROME

WEEKLY CLINICAL CONFERENCE

By Invitation: Leonard B. Berman, M.D.*
Case: Catherine Chester, M.D.†

The following case is presented in order to bring to attention the various aspects and ramifications of the nephrotic syndrome. Dr. Leonard Berman from the Department of Renal Diseases, Georgetown University School of Medicine will discuss the newer concepts in the etiology and treatment of this entity.

CASE REPORT

D. C., an 18 month old colored girl, was first admitted to Children's Hospital on February 29, 1956 with a history of swollen eyes for one week and an upper respiratory infection for one day. At the time of admission she appeared to be well developed and well nourished but quite irritable. There was pronounced periorbital edema. Her blood pressure was 140/85. Admission weight was 25 pounds, 6 ounces. Admission rectal temperature was 100 F.

Admission hemogram was normal. Many urinalyses during hospitalization revealed from 1000–3000 mg. of albumin per 100 ml., specific gravities ranging from 1.015 to 1.030, red cells and 4–10 white blood cells per high power field. Blood cholesterol was 600 mg. per 100 ml., and blood urea nitrogen 8 mg. per 100 ml. The antistreptolysin "O" titer was under 12 units. Total proteins were 5.2 gm. per 100 ml. with A-G ratio of 2.7/2.5. X-ray of the chest was normal.

The patient was put at strict bed rest, given a low salt diet and daily procaine penicillin therapy. On this regime, she gradually lost her periorbital edema and, when discharged, weighed 22 pounds, 12 ounces. She became much brighter and

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more alert. Her blood pressure fell to normal levels (100/80). She was discharged on March 23, 1956, given oxytetracycline for prophylaxis, and referred to the Out Patient Department for follow-up. During her hospital stay, her urine was never free of albumin and her urinalysis at discharge contained 1200 mg. per 100 ml. of albumin together with 3–5 red blood cells and 3–5 white blood cells per high power field.

She was readmitted on June 11, 1956 because of generalized edema. There was marked periorbital edema, ascites and 2 plus pitting edema of the ankles. Her blood pressure was 120/88. Admission weight was 34 pounds, 8 ounces. The urine contained 3000 mg. albumin per 100 ml., and 5–6 white blood cells, and 3–8 red blood cells per high power field.

During this hospitalization, her low salt diet and oxytetracycline therapy were continued. In addition, on June 12, 1956 she was given 40 mg. of prednisone daily. This dose was gradually reduced and discontinued on June 27, 1956. Urine on this date contained no albumin, 5–8 red blood cells and 3–8 white blood cells per high power field. Urine specific gravity was 1.030. Coincident with the disappearance of albumin from the urine she began to diurese and lost her edema. Her weight fell to 24 pounds, 10 ounces. On July 1, 1956, however, her urine again contained 250 mg of albumin per 100 ml. and this has gradually increased until now random specimens of urine contain 2000 mg. of albumin per 100 ml. She is currently receiving 20 units of ACTH daily.

DISCUSSION

Dr. Berman:

Our knowledge of nephrosis or the nephrotic syndrome has rapidly advanced in recent days. This is partly due to the use of needle biopsy of the kidney, and a great deal of it comes from experimental production of the nephrotic syndrome. It is always a great help in elucidating mechanisms in disease states when one can reproduce it in animals, and as you know, there are now various species in which a nephrotic syndrome closely resembling that of man, can be produced.

In talking to a group of pediatricians one ought first to begin with the time honored argument of whether lipoid nephrosis, or, as it is sometimes called, "pure" nephrosis, constitutes a separate disease entity, or rather a phase of glomerulonephritis. Historically this argument began with the observation by several excellent clinicians that there was a nephrotic syndrome which clinically was of insidious onset and not associated with obvious infection, streptococcal or otherwise. More importantly, when these children and adults died, (and many times they died of infection, not of renal disease), at post mortem examination, their glomeruli were considered to be normal or minimally involved. Because nobody from 1900 up to 1930, was willing to concede that a typical post-streptococcal acute glomerulonephritis which went on to be associated with the death of the patient, could be associated with normal glomeruli at autopsy, the champions of the lipoid nephrosis or "pure" nephrosis school had a strong argument.

The first break in the picture came about twenty years ago when, with use of special stains, pathologists, particularly Bell, began to insist that these glomeruli were not normal, but had slight thickening of the basement membranes. Gradually more pathologists have been won over to this view.

This, however, did not convince those who wanted to keep lipoid nephrosis as a distinct entity, quite apart from post-streptococcal glomerulonephritis, and I think, one of the first definitive pieces of information was in an article by Moschowitz. This observer followed a child who began his clinical course with an acute glomerulonephritis, completely typical in every way, (blood in the urine, swollen eyelids, hypertension). The child then went on to have a nephrotic syndrome, associated with hypertension and red cells so that he would still be called a glomerulonephritic. In the course of two or three years he was readmitted with a "pure" nephrotic syndrome, no hypertension, no azotemia, and no abnormal urine sediment. This child died, and his glomeruli showed precisely the same minimal changes of basement membrane thickening which many pathologists would have passed over as normal.

There we have our first real proof that what clinically is typical, unmistakable, post-streptococcal glomerulonephritis which goes on to a "pure" nephrotic syndrome, may be associated at post-mortem with almost normal glomeruli or slight thickening of the basement membrane.

In recent days, here in the District, Dr. Parrish at Mt. Alto Hospital has been doing kidney biopsies on patients with acute glomerulonephritis, and he has periodic kidney sections up to three years after the onset of the disease in its "typical" form. He has confirmed, in about five people, Dr. Moschowitz's findings of some years ago, that such patients are frequently left with only basement membrane thickening. Now what does this prove? It proves that post-streptococcal glomerulonephritis may end up with exactly the same kind of glomerular changes as those so-called "pure" lipoid nephrosis. It does not prove, by any manner of means that the child who begins with a "pure" nephrosis and goes on to whatever his fate will be, is necessarily post-streptococcal. It does, however, render untenable the argument that because a child begins with lipoid nephrosis and ends up at autopsy with glomeruli that are minimally involved, he could, therefore, not have started with post-streptococcal glomerulonephritis. We know now that this is definitely not true.

So much for historical perspective. We have been interested in the nephrotic syndrome from an etiologic point of view, and there are now perhaps a dozen or so well established etiologies. Most of our work has been with adults, but because the nephrotic syndrome, in whatever setting it occurs, has so much in common with the nephrotic syndrome of another setting and another etiology, it is reasonable to discuss something about

this syndrome as it applies to children with no evidence of renal insufficiency or hypertension.

Clinically, I think the place to begin is with the urine sediment, and over the course of several months we have been taking pictures whenever we could of nephrotic sediments. Perhaps the hallmarks of nephrotic urine sediments are renal tubular epithelial cells from the convoluted tubules, greatly swollen and distended with fat. This fat when examined in reduced light shows up as very shiny, highly refractile little droplets. When fat appears in this form, that is, encased within a tubular epithelial cell, the cell is called an oval fat body. A nephrotic, whatever the etiology, may be expected at some time or other to show oval fat bodies, i.e., desquamated epithelial cells which are swollen with fat.

The reasons and mechanisms for fatty degeneration of epithelial cells are still unknown, but it has been pointed out that in a great many non-renal conditions which are associated with hyperlipemia, particularly starvation or sprue, the same sort of condition may be found. Therefore, some people believe that the presence of hyperlipemia is enough explanation. This is by no means a settled question. If one examines these fat droplets under polarized light one may see the fat deposited in one of two forms, either as neutral fat or as esterified cholesterol. The esterified cholesterol produces the so-called "doubly refractile fat body" or "maltese cross". (Figure 1)

FIG. 1. Doubly refractile fat body in nephrotic urine examined under polarized light

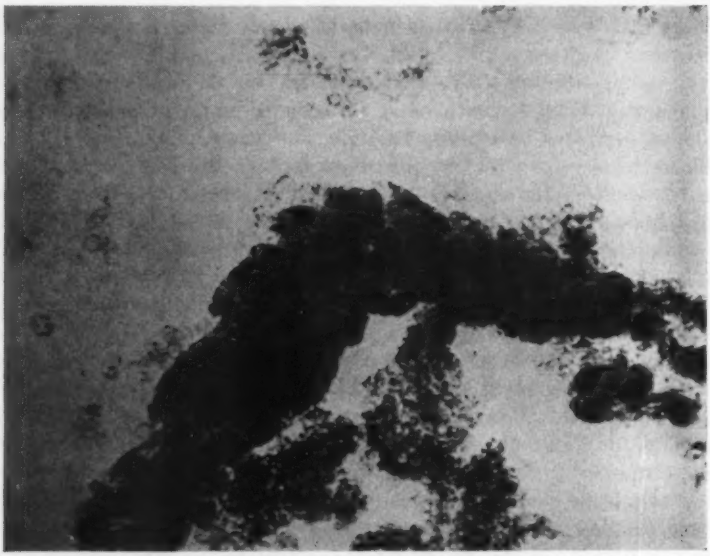

FIG. 2. A renal epithelial cell cast often found in nephrotic urine

Another characteristic of nephrotic urine is the shedding of large numbers of epithelial cells. When these cells are shed *en masse*, when they strip a whole portion of a tubule, they produce an epithelial cell cast. (Figure 2) The cells later degenerate and pretty soon they become coarsely granular. The final step in their evolution is to become the so-called "waxy" cast. These urine sediment findings are common to the nephrotic syndrome, regardless of its etiology.

The blood chemistries of a nephrotic patient, whatever his background, have certain things in common. Let us start with the hyperlipemia, because there has been a great deal of recent work on nephrosis which partially elucidates the mechanism whereby a nephrotic becomes hyperlipemic. In the first place, this hyperlipemia is confined to plasma. These animals and patients do not have fat loaded tissues. On carcass analyses one finds that this excess cholesterol is entirely in the plasma. It has been found that there is no alteration of the rate at which cholesterol is synthesized in the nephrotic, but there is a great change in the rate at which it is transported from plasma to liver. Once it gets to the liver, it is degraded to bile acids at a normal rate, so that the block, if we can speak of it that way, has been now localized very sharply to a transport mechanism in plasma.

What transport mechanism could this be? A series of papers by Friedman and Rosenman in California, will shed some light on this. They began with the premise that if the transport mechanism were disturbed, some protein

in the plasma may be the site of the disturbance, and the logical substance to begin with was the serum albumin. They took a series of rats and gave them nephro-toxic sera which would consistently produce a nephrotic syndrome with a rise in cholesterol, but they prepared these rats in a number of ways, all of which led to the prevention of loss of albumin in the urine. That is, they implanted the ureters into the inferior vena cava or tied the renal pedicle, or used any one of a number of other techniques to prevent protein loss in the urine. They then found that their animals developed the nephrotic syndrome, clinically and morphologically, but had no rise in plasma cholesterol. They went one step further. They took animals in whom albumin loss was not prevented by the experimental situation, gave them nephro-toxic sera, and then infused albumin at a rate which equalled the amount lost. These animals did not develop hyperlipemia.

They next went to humans and began to do statistical surveys, correlating hyperlipemia, not with total protein as had always been done in the past, (with very poor correlation), but with accurate measurements of serum albumin. They say that the correlation is good, although this awaits confirmation.

At present, I think one reasonable hypothesis with some evidence behind it is that the nephrotic keeps making cholesterol at a normal rate, but piles it up in his plasma because he cannot get rid of it. He cannot get rid of it because its transport mechanism into bile is disturbed, and this may be related to a quantitative deficiency of serum albumin. It is interesting that Dr. Addis suggested this 15 years ago, but like so many good ideas, it had to wait until someone could get around to proving or disproving it.

Sometime ago, we began to study nephrotic syndrome, in adults mainly, from this point of view: if we could define the early glomerular changes, and make specific etiologic diagnoses, we could then develop a body of data relating to the effectiveness of one therapeutic technique over another, depending on what kind of nephrosis we were dealing with. Secondly, we hoped we could elucidate the frequency of incidence of nephrotic etiologies and perhaps uncover new nephrotic etiologies. This work is actively going on by means of examination of renal biopsy material.

Biopsy material looks quite different from pathologic material, and for the first six months we had quite a lively time with our pathologists. They were not very used to looking at glomerular membranes from the living patient. The point is that such a glomerulus has very delicate, lacy, capillary loops with no smudging of these loops. They are very distinct, sharp and discrete. The tubules are orderly, and lie back to back with only the basement membranes between them. Their epithelium extends over their entire circumference.

The kind of glomerular change which has been described in the past in

children dying with lipoid nephrosis, and also the kind of glomerular change that Dr. Moschowitz described in his one child, is a thickening or "smudging" of the glomerular loop. We classify it now as a membranous glomerulonephritis. This change is also what Dr. Parrish is finding years after an attack of acute glomerulonephritis due to beta hemolytic streptococci.

With that as a background we can turn to the patient this morning. It is interesting that she is a colored girl. The experience around the country has been that the nephrotic syndrome is relatively uncommon in Negroes. This is not true in adults. We have many of them, but I will have to ask you if it is true in children. It is not true here? Then I think that some people with insufficient statistics have been reporting.

Now her age: her disease began at 12 months of age. In the past, people have taken children with lipoid nephrosis and children with glomerulonephritis who were nephrotic, and have scrutinized every possible bit of information about their clinical courses side by side to see if they could develop criteria for separating them. It has been shown that lipoid nephrosis generally begins at a considerably earlier age, that is, about a year or a year and a half, sometimes even sooner, than frank glomerulonephritic nephrotics. I think that this may be true for the series reported, but I do not think it constitutes any very strong evidence for the separate identities of these two kinds of nephrotics. Glomerulonephritis has been reported *in utero* and we see, not a great number, but we see some children with frank glomerulonephritis in this early age group.

We feel that the hallmark of the nephrotic syndrome is proteinuria, usually more than 5 grams per day. With any specific figure, you are immediately confronted with the many exceptions but over 5 grams is a good rule. We have nephrotics who are putting out 2 grams, but there are other reasons for feeling sure that they are nephrotics. The other criterion I think we can insist on for a diagnosis of the nephrotic syndrome is the presence of either doubly refractile fat bodies or oval fat bodies in the urine. We have yet to see a nephrotic who lacks them.

If these two criteria are satisfied we do not demand any others. A nephrotic does not have to be edematous, or hyperlipemic, or hypoalbuminemic. These things take time to occur and I can show you records of having to wait two years before elevated blood cholesterol developed in a nephrotic we were watching.

This little girl's disease began with periorbital edema but I think she saves us a great deal of argument because she was admitted with what seems to be fairly clearcut evidences of nephritic nephrosis. She is hypertensive and she consistently has red cells in her urine. She lacks one thing. The case would be complete if we could demonstrate red cell casts as well as red cells in her urine, in other words, undeniable evidence of blood arising

from the upper nephron. She is also reported as having white cells in her urinary sediment. That is hard to interpret. Were these tubular epithelial cells, which most technicians call white cells? Were they polymorphonuclear cells? If they were these latter cells, does this mean anything diagnostically? The answer is that a patient with nephrosis who also has acute glomerulonephritis puts out large numbers of polymorphonuclear cells; he has literally a pyuria; if you will, has pus cells in casts; and has glitter cells. As you know, when glitter cells were first described, the evidence suggested that these cells were specific for pyelonephritis but we did a study on 8 children all of whom had definite acute glomerulonephritis. All had large numbers of glitter cells and all had pus casts in their urine.

She was administered a low salt diet. The low salt diet is something agreed upon by anybody treating the nephrotic syndrome. These patients have been found to be putting out very high levels of aldosterone in their urine, and their sodium conservation mechanisms are maximal. The amount of sodium in a nephrotic urine is very low, about five milliequivalents per liter. This is quite extraordinary when you consider that casual urine specimens of normal people will contain sodiums of 150 or 160 milliequivalents per liter. Added sodium in the diet, therefore, obviously provides building blocks for edema.

When she was discharged from the hospital for the first time she still had a large quantity of urinary protein and fairly active urinary sediment. This of course is the type of patient in which you would expect a rather rapid relapse of edema, and it is not surprising to find that she was readmitted with pretty much the same picture.

This patient is classical in that her serum cholesterol is elevated, but if it were normal it should not sway you in the diagnosis at all. Other patients show the curious phenomenon of an elevated serum cholesterol only after diuresis. It is as if the lipo-protein to which cholesterol is bound (mainly beta-lipoprotein) is diluted, or as if it has an apparent concentration which is below its true one. Be that as it may, we have a number of times observed that serum cholesterols will rise from the first time only after a drying out.

She has a fast sedimentation rate, and this is one of the most characteristic things about a nephrotic. Almost all of the proteins of the blood can pass through a nephrotic glomerular membrane except fibrinogen. This leaves a relatively increased concentration of fibrinogen and a fast sedimentation rate.

Serum albumin again is usually low in the nephrotic, but it may be normal. Reduction in serum albumin comes with time. When we see the child, serum albumin levels may not be decreased, and we have had to wait as long as three or four months before the decrease became evident. Whether

a nephrotic can synthesize as much albumin as the normal is at the moment controversial.

Her blood urea nitrogen is normal which is not at all unusual in the nephrotic child. To me it would merely mean that this child was a lot more nephrotic than nephritic. When you have a mixed picture one or another of the manifestations may be emphasized. Any given patient may have a very active glomerulonephritis and a full blown nephrotic syndrome if he is that unfortunate. He may have only one or two nephrotic features with a very active nephritis, or he may have very little nephritis, but a great deal of nephrosis.

Finally, steroid therapy: with all the work that has been done on steroid treatment of the nephrotic syndrome you have only to read any of the Proceedings of the Conference on Nephrosis, or any other articles relating to treatment, to see that the past five years have not produced enough data. With all the people investigating steroid therapy and with all the effort that is being made, each investigator still has his own particular mode of treatment, his own time-dose relationship, his own favorite drug. Until a uniform body of data on etiologically diagnosed nephrotics is available I see no hope for improvement. Our own series has been treated mainly by ACTH; other authors have treated nephrosis entirely with cortisone, and still other people with hydrocortisone. The delta-steroids are still far too new to evaluate.

While receiving steroid this patient had a diuresis. This, per se, means very little since a nephrotic may have a diuresis spontaneously or by contacting any one of a number of infections, except upper respiratory infections. It is peculiar that cellulitis, empyema, and measles, may all cause diuresis in a nephrotic child, but an upper respiratory infection will not. More important, when we treat a nephrotic with steroids, urine protein clears, (and this may happen before the diuresis); we have perhaps truly improved the disease. We say this because the nephrotic syndrome may well be primarily a glomerular membrane disease, and many of the manifestations result from the loss of urine protein. It is true that steroids in a great number of cases can produce a disappearance of urine protein. When this happens, if one waits a little while, one will usually also get a drop in serum cholesterol and a rise in serum albumin.

This child, unfortunately, clearly relapsed in a very short period of time. Why? My answer would be that she is a nephritic nephrotic, and the chances of treating her successfully are fairly poor. Such a child may live two years; she may not. I am not prognosticating for this child. No one can guess at a prognosis early in the course of the disease. It is not surprising to me that she has relapsed.

What should you do now? I assume that evidences of persistent strepto-

coccal infection have been looked for. What you do depends upon what part of the disease you are treating. You cannot just go ahead and say, "We will treat her". Are you treating her edema? Do you want to produce a diuresis? If so, you may accomplish it with Diamox ®, with a prolonged course of intravenous serum albumin, with a low salt diet over a period of time, or with an intercurrent infection. All these may cause a diuresis. Do you want to do what you can about her glomerular membrane defects? About the only thing we really know of, outside of spontaneous remissions, are steroids. Has she had a sufficient course of steroids? Some people, particularly Arthur Merrill at Atlanta, who has had a large experience with nephrotics might advise the use of larger doses for a longer time. Our tendency has been to back off when we have a nephritic-nephrotic who does not do well with the first course of steroids. This is not an answerable question as far as I know, and I really will leave it up in the air. You have your choice between non-specific diuretic measures, "full speed ahead" with another vigorous course of steroids, or waiting, talking to people who are working in the field and deciding on some other course of action.

CLINICAL PATHOLOGICAL CONFERENCE

Directed by : E. Clarence Rice, M.D.,* Grace H. Guin, M.D.†
Discussed by: John E. Cassidy, M.D.,‡ Joseph M. LoPresti, M.D.§

Clinical Summary: This 2½ year old colored girl was well until a week prior to admission, when she began to complain of abdominal pain. Five days prior to admission she began to vomit. Her mother had noticed round worms in the child's stools so the patient was taken to another hospital five days prior to admission, where she was treated with "worm medicine". The day prior to admission she vomited a worm. She had been weak and irritable for two days and still complained of abdominal pain. There was no fever, cold, or diarrhea, and no blood was seen in the stools.

Family History: Non-contributory.

Physical examination: On admission the patient was a well developed,

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well nourished 2½ year old colored girl appearing acutely ill, lethargic, and irritable. Her temperature was 99 degrees, pulse 120, respirations 20, and blood pressure 110/80. There was moderate dehydration. The neck was supple. The eardrums were slightly inflamed. There was a mucoid nasal discharge, and the pharynx was moderately erythematous. The lungs were clear to percussion and auscultation. The abdomen was soft, no pain or tenderness was noted, and the liver and spleen were not palpable.

Laboratory Data: Urinalysis: Color, clear; pH 5.5, albumin and sugar negative; acetone 2 plus. Hemogram: Hemoglobin 8 grams, hematocrit 29 per cent, WBC 17,900; differential: segmented 71, bands 3, lymphocytes 20, monocytes 3, eosinophiles 3. Platelets were adequate. There were many stippled red cells present; a few target cells with an occasional polychromatic red cell were reported. Two nucleated red cells per 100 white cells were counted. There was no sickling.

Clinical Course: On admission 200 ml. of Ringer's solution, followed by 500 ml. of 5 per cent glucose in physiologic salt solution were given intravenously. This was followed by 500 ml. of Butler's solution. An initial intramuscular dose of 800,000 units of aqueous procaine penicillin was injected and this was repeated every 12 hours. Sodium phenobarbital was given orally every four hours for sedation. Oxygen was administered. Irritability increased, and she lapsed into coma. Blood pressure was 156/100. She became unresponsive and died 35 hours after admission.

DISCUSSION

Dr. Cassidy:

I would like to consider first the picture up to the presentation of laboratory data. In summary, we have a 2½ year old colored girl, who has had abdominal pain for a week, who has been vomiting for five days, and who had round worms in her stool. I presume that these were *Ascaris lumbricoides*, for which she had been treated, the nature of the therapy being unknown. On admission she was acutely ill and irritable. She had a blood pressure of 110/80, which if it was carefully taken under as nearly basal conditions as possible, would have to be considered as being elevated.

This part alone, of course, brings up many diagnoses for consideration. I think that the first one we will consider will be the worm infestation due to the fact that it was quite obvious. Infestation with *Ascaris* usually is a minor clinical problem. It is unusual for it to produce severe symptoms, although youngsters can have colicky abdominal pain, urticaria, cough and at times, pneumonia. It would be unusual for infestation to produce the extreme clinical picture which was present in this patient. It is possible, however, for a youngster with an overwhelming infestation with worms, who has been treated and has not eliminated the worms, to become very toxic from the breakdown products which are absorbed.

In any youngster with abdominal pain one must consider the inflammatory conditions which could produce this picture, such as appendicitis, peritonitis, and mesenteric adenitis. In the negro patient one must think of sickle cell anemia. In view of the elevated blood pressure, one must consider various renal disorders, such as acute nephritis, infections of the urinary tract, or genito-urinary tract anomalies. For the sake of completeness one should also consider the allergic types of purpura, although there should ordinarily be other findings such as joint manifestations or petechiae of the skin and mucous membranes.

Of course, the condition which we have all become very conscious of is intoxication with heavy metals, the most common of which is lead poisoning. It would not be unusual at all for lead poisoning to cause such a clinical picture as this. With lead intoxication as severe as this, one would expect convulsions in a high percentage of cases, although this is not essential.

I think that those are the main considerations on the basis of the history and physical examination. We assume that everything is given in the protocol. If, in addition to that, we consider the laboratory data, it will narrow the field down. The urinalysis is within normal limits except for the presence of acetone, which does not help in any particular way, but of course could go along with many conditions. The hemoglobin of 8 grams with a hematocrit of 29 per cent demonstrates a very definite anemia which is on the hypochromic side. There is a leukocytosis with a shift in the neutrophils for a youngster of this age, and 3 per cent eosinophiles, which is fairly close to the normal range. Platelets were adequate. The morphology and characteristics of the red blood cells are important. There were many stippled erythrocytes, and a few target cells, with some polychromatophilia and normoblasts. This indicates that there is increased erythropoietic activity. This is present in many types of anemia. The sickle cell preparation was reported as negative. This is not conclusive, if but one preparation were examined. The stippling of the red blood cells, although it can be seen in many conditions in which there is stepped-up activity in erythropoiesis, certainly would bring to mind very strongly the possibility of lead intoxication.

The clinical course of the patient in the hospital was a rapidly downhill one; despite measures for hydration and sedation the patient expired in a short period of time. Again, the blood pressure is significant, because it certainly was elevated before the patient expired.

One group of disorders which have not been considered are those of the central nervous system. These could give a picture similar to that seen in this patient. The inflammatory ones, such as tuberculous meningitis, any of the encephalitides, could give this picture. Of course, neoplasms of the central nervous system, either primary or metastatic, could produce the same set of symptoms.

I think that the one diagnosis which seems to fit this picture would have to be lead poisoning. In this age group, which is the common age group for such a condition, although there is no history of pica, one could probably assume that if the child could acquire round worm infestation, the chances would be rather good that she could also have been ingesting substances containing lead. The weakness and irritability, the lapse into coma, the hypertension, the anemia, the stippling of the erythrocytes, all would certainly fit in with this diagnosis and, of course, the fact that the patient died would have to be considered in the diagnosis too, against some of the other diagnoses which we have mentioned which do not ordinarily result in death. Sickle cell anemia would have to be kept in mind even though the sickle cell preparation was reported as negative, and it would certainly be very unusual for a course such as this to have occurred with uncomplicated sickle cell anemia. I think that we have to mention once again the worm infestation, just on the very remote possibility that this patient did have an overwhelming infestation and that it was treated, and a severe toxic type of reaction resulted which was secondary to the treatment, not necessarily to the drug used, but due to the destruction of the parasites. I think that we should mention for the sake of completeness that drugs that are used as vermifuges at present are relatively non-toxic. I am assuming that this patient was treated during the past 18 months or two years.

Dr. LoPresti:

The radiologist can often suggest the diagnosis of heavy metal intoxication. The changes that you can see are the increased densities at the epiphyseal plates with widening of the metaphyses. I would point out one precaution however. These lines are not characteristic of lead. First of all, the lines are not due to the presence of a large amount of lead in that area. The lead in the bone is deposited throughout the whole bone. The lead lines form due to the interference of growth with increased trabeculation. There is no more lead in the metaphyseal region than in any other portion of the bone. Other conditions which can produce exactly the same changes are other heavy metals, such as lithium, bismuth, and phosphorus. You can see these changes in normally rapidly growing bone, and lastly, you can see these same changes in healing rickets. All that the radiologist can say is that this is suggestive of heavy metal poisoning.

Dr. Guin:

At autopsy we found a good deal of pulmonary edema, but there was no pneumonia or other significant change. The brain was slightly below normal in weight. The microscopic examination did not show any alteration. The chief findings were noted in the liver and kidneys. The convulsions and cause of death, were no doubt both due to hepatic failure. Virtually every

hepatic cell was intensely vacuolated. We did special stains which ruled out fat and identified the material as glycogen, so there was marked interference with liver function. In cases of lead poisoning acid-fast bodies have been found in the nuclei of hepatic cells. We do not know if these represent degenerating molecules of desoxyribose nucleic acid, but whatever the material is, it takes the acid-fast stain and is found also in the cells of the proximal and distal convoluted tubules of the kidney. We observed acid-fast bodies in this material. The remaining organs were not remarkable. The tissue was macerated and was examined for lead. The bones contained the largest amount of lead. I did neglect to mention one thing. The costochondral junction showed increased bony trabeculation with a thickening of the cartilage which would corroborate the roentgen findings in the long bones. On microincineration of this area lead was not identified. However, when the bone from a lumbar vertebra was macerated and assayed it contained more lead than was found in any other portion of the body. The organs containing the next largest amounts of lead were the kidney and liver. It was also of interest that the brain was reported to contain no lead. I have no explanation for that. We were able to corroborate indirectly, at least by histopathological technic and the chemical determination of the individual organs, the diagnosis of lead poisoning.

Dr. LoPresti:

To me the most interesting thing about this condition is that in 1951 almost everyone here became interested in cases of lead poisoning and started to look for them. Over 90 per cent of the cases have been diagnosed since 1951. I am sure that this diagnosis has been overlooked and in large number. I think that second to salicylate poisoning, this is the commonest intoxication in childhood. In children the outstanding feature is the encephalitis.

Dr. Guin:

If other cases do not show any lead in the brain, we would have to postulate that this child had hepatic coma.

Dr. LoPresti:

You are intimating that the changes in the central nervous system are due to actual deposits of lead in this portion of the body. I would like to hear what Dr. Rice has to say about the changes noted in the brain.

Dr. Rice:

The brain in cases of lead encephalopathy is reported as showing edema uniformly, with variable reports of thickening of the arachnoid, with changes in the small blood vessels of the brain consisting of endothelial

and adventitial proliferation, and with reduction in the caliber of the vessels. The walls of the small vessels may show some evidence of calcification. Perivascular and perineural gliosis is also seen. Microglia are reported to be increased, especially in the cerebellum. Some of the symptoms are thought to be due to spasm of the blood vessels with resulting anoxia. Changes in the peripheral nerves are limited to degeneration of axis cylinders and myelin sheaths, with proliferation of the sheath cells of Schwann. There is no question that the index of suspicion of a hospital staff will be the determining factor in making the diagnosis of rather obscure diseases such as lead intoxication. The reported differences in the frequency with which lead poisoning is seen in various hospitals is undoubtedly due to whether or not this intoxication is looked for. Dr. Samuel Bessman's interest in the diagnosis and therapy of lead poisoning served greatly to increase the interest of the medical staff in this disease. Dr. LoPresti might like to comment on the therapy of this toxemia.

Dr. LoPresti:

The treatment of choice for lead poisoning is calcium versenate, EDTA, ethylenediamine tetra-acetic acid. This is a chelating agent which combines with the lead and forms a non-toxic substance which is rapidly eliminated. It is used parenterally and must be diluted with 5 per cent glucose in distilled water. The daily dose is 30 mg/kg. This is given in three divided doses by clysis. Each dose amounts to between 160 and 200 ml. The drug is given over a period of five days and is repeated over another period of five days after a three day rest period. It should not be given orally, as the versenate will combine with the other heavy metals in the intestinal tract.

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